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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

[Continued on next page]

(54) Title: METHODS AND KITS FOR DIAGNOSING AND TREATING B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA  
(B-CLL)



AMB1

Human IL4

WO 2004/046376 A3

(57) Abstract: The present invention relates to methods and kits for detecting several polynucleotide sequence found to be indicative of a poor prognosis of B-CLL. All the polynucleotides are transcribed from a region on human chromosome 12p21-22. Most of the polynucleotides do not encode larger polypeptides, but may encode small peptides, they may function as RNAs. Four polynucleotides encode a novel protein, which in one preferred embodiment can be used as a cytokine, preferably as an interleukin. Furthermore the invention relates to methods and compositions for treating B-CLL in particular poor prognosis B-CLL.



ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00794

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C12Q1/68	G01N33/50	G01N33/574	G01N33/68	C12N15/12
	C12N15/85	C07K14/47	C07K16/18	C12P21/00	A61K31/7088
	A61K38/16	A61K39/00	A61K39/395	A61K48/00	

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q G01N C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, Sequence Search, EMBL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DAMLE R ET AL: "B-cell chronic lymphocytic leukemia cells express a surface membrane phenotype of activated, antigen-experienced B lymphocytes"            BLOOD,            vol. 99, no. 11, June 2002 (2002-06),            pages 4087-93, XP002248139            the whole document</p> <p>-----</p> <p>KRÖBER A ET AL: "VH mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia"            BLOOD,            vol. 100, no. 4, August 2002 (2002-08),            pages 1410-16, XP002248141            cited in the application            the whole document</p> <p>-----</p> <p>-/-</p>	1-7
A		1-7

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

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Date of mailing of the international search report

16/08/2004

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIN K ET AL: "Relationship between p53 dysfunction, CD38 expression, and IgVH mutation in chronic lymphocytic leukemia" BLOOD, vol. 100, no. 4, August 2002 (2002-08), pages 1404-09, XP002248142 cited in the application the whole document -----	1-7
A	OSCIER D ET AL: "Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors" BLOOD, vol. 100, no. 4, August 2002 (2002-08), pages 1177-84, XP002248143 cited in the application the whole document -----	1-7
A	WO 00/44788 A (HARIHARAN KANDASAMY ;LABARRE MICHAEL J (US); HANNA NABIL (US); HUY) 3 August 2000 (2000-08-03) claim 19 -----	
A	DATABASE EMBL 'Online! Homosapiens 12 BAC RP11-693J15 26 April 2000 (2000-04-26), MUZNY D ET AL: "Homosapiens 12 BAC RP11-693J15" XP002248623 retrieved from EBI Database accession no. AC063949 99.8% identity in overlap of 1959 nt of SEQ ID NO 2 (1935-3893) to nucleotides 56450-58408 of AC063949 -----	8
A	WO 01/64886 A (CORIXA CORP) 7 September 2001 (2001-09-07) -----	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 34 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Claims Nos.: 16-25

Present claims 16-25 relate to use of and methods for treatment in which both make use of a compound defined by reference to a desirable characteristic or property, namely the compound is capable of eliminating transcription of at least one of the expression products defined in terms of their SEQ ID Nos.

The claims cover all compounds, *inter alia* ribozymes (see description) and si-RNA (claim 25) having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has not been carried out for the above mentioned claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK 03/00794

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 16-25  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 34 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: 16-25  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/DK 03/00794

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0044788	A 03-08-2000	AU 3473100	A	18-08-2000
		CA 2359994	A1	03-08-2000
		EP 1157042	A1	28-11-2001
		JP 2002536969	T	05-11-2002
		WO 0044788	A1	03-08-2000
WO 0164886	A 07-09-2001	AU 4347701	A	12-09-2001
		WO 0164886	A2	07-09-2001
		US 2003078396	A1	24-04-2003
		US 2004002068	A1	01-01-2004
		US 2004005561	A1	08-01-2004
		US 2002198362	A1	26-12-2002